Synthesis and antibacterial activities of Diarylpyrazolo [3,4-*b*]*pyridines II*[1]

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Síntesi i activitat antibacteriana de Diarilpyrazolo [3,4-b] piridines II[1]

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RESUMEN

Se presenta la síntesis de diversas 4,6-diarilpyrazolo[3,4-b]piridinas, a partir de aminopirazoles y 1,3-dicarbonil derivados o por un método de Doebner.

Palabras clave: aminopirazoles; diarilpyrazolo [3,4-*b*] piridinas; método de Doebner.

ABSTRACT

Synthesis of various 4,6-diarylpyrazolo[3,4-*b*]pyridines, from aminopyrazoles and 1,3-dicarbonylcompounds or by a Doebner method are reported.

Keywords: Aminopyrazoles; diarylpyrazolo[3,4-*b*] pyridines; Doebner's method.

RESUM

Es presenta la síntesi de diverses 4,6-diarylpyrazolo [3,4-b] piridines, a partir de aminopirazols i 1,3-dicarbonil derivats o per un mètode de Doebner.

Paraules clau: aminopirazols; diarilpyrazolo [3,4-b] piridines, mètode de Doebner.

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INTRODUCTION

A number of substituted pyrazolo[3,4-*b*]pyridines have been reported and a variety of these have been synthesized because of their potential biological activities such as xanthine-oxidase inhibitors, anti-microbial and anti-inflammatory agents [2]. Some fluorinated tetraarylpyrazolo[3,4-*b*] pyridines have been reported to act as nervous system depressants and anti-inflamatory agents[3], Our continuous interest in the chemistry of this ring system[1,4-6] led us to report the synthesis of the parent ring system by decarboxylative rearrangement of 3-cyanopyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid[5] and their electrophilic, nucleophlic and homolytic reactions were reported previously[1]. More recently reactions of some aminopyrazoles with mono and diketo compounds leading to aryl and diarylpyrazolo[3,4-*b*]pyridines have appeared[7-9] and this prompts us to report our results on the synthesis of various diaryl pyrazolo[3,4-*b*]pyridines. A general method of building a pyridine ring on to a pyrazole nucleus via reaction of 5-aminopyrazoles with 1, 3-dicarbonyl compounds in the presence of zinc chloride was earlier reported[10]. This method however failed when dibenzoylmethane was used as a 1,3-dicarbonyl component, a zinc complex[11] being formed instead.

EXPERIMENTAL

The proton NMR spectra were recorded on a Hitachi-Perkin Elmer MODEL R-20-B(60MHz) and a Bruker AM 300 spectrometer (Rheinstetten–Forchheim, Germany) operating at 300 MHz, respectively using $CDCl_3$ solvent with tetramethylsilane(TMS) as an internal standard. The infrared spectra (IR) were taken on a Perkin-Elmer model 180. Samples were measured as potassium bromide disks. Melting points were obtained on Fisher Johns and Gallenkamp apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 2400. The 5-aminopyrazole used in these reactions was prepared according to the literature method stated earlier[1]. All the reagents and solvents used in this work were of analytical grade and purity.

General Methods

Method A

A mixture of a 5-aminopyrazole (5mmoles) and 5mmoles of dibenzoylmethane in 5mL of acetic acid was heated under reflux for a period of 16-48 hours. Excess of acetic acid was removed and after cooling, the reaction mixture was inverted over crushed ice, basified with ammonium hydroxide, filtered and recrystallized from a suitable solvent to obtain the desired product.

3-methyl-1-(4-nitrophenyl) 4, 6-diphenyl-1H**-pyrazolo[3, 4-**b**]pyridine (1),** this compound was obtained in 60% yield; M.P. 210-212 °C; IR (KBr) (v, cm^{-1}): 3060, 1600, 1595, 1560, 1510, 1330 (NO_2) , 840, 810, 760; ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 2.28(3H,s,CH_3); 7.34-8.22 (11H,m,H-5&ArH); 8.24-8.44(2H,dd) N-aryl.H, 8.64-8.88 (2H,dd) N-aryl.H. Anal.Calcd.for $C_{25}H_{18}N_4O_2$ (Mw 406) C, 73.98; H, 4.46; N, 13.78.Found C, 73.90; H, 4.35; N,13.81.

3-methyl-1, 4, 6-triphenyl-1H**-pyrazolo[3,4-**b**]pyridine (2),** 65% yield; M.P. 149-151 °C; IR (KBr) (v, cm^{-1}): 3040 ,2920,1600,1560,1500,930,840,750,690; ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 2.28(3H,s,CH_3);7.18-7.66&8.06-8.58 (16H,m,H-5& Ar-H) Anal.Calcd.for $C_{25}H_{19}N_3$(Mw 361) C, 83.08; H, 5.30; N,11.62.Found C, 82.83; H, 5.32; N,11.64.

1-(4-chlorophenyl) 4, 6-diphenyl-1*H*-pyrazolo[3,4-*b*] pyridine (3), 78% yield; M.P. 174-75 °C; IR (KBr) (v ***cm^{-1}):*** 3100, 3060, 1590, 1560, 1500, 930, 820, 740,680 ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 6.83(1H,s,H-3);7.32-8.56(15H,m, ArH&H-5)

Anal.Calcd.for $C_{24}H_{16}ClN_3$ (Mw 381) C, 75.62; H, 4.23; N, 11.02.Found C, 75.42; H, 4.42; N, 10.79

3-methyl-1-(2-chlorophenyl) 4, 6-diphenyl-1*H*-pyrazolo [3,4-*b*]pyridine (4), 64% yield; M.P. 153-54 °C; IR (KBr) (v ***cm^{-1}):*** 3060, 3030, 2960, 2920, 1580, 1570, 1560, 1500, 1480, 1380, 760, 750, 700, 690. ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 2.34(3H,s,CH_3);7.30-8.24(15H,m, ArH&H-5) Anal. Calcd.for $C_{25}H_{18}ClN_3$ (Mw 395) C, 75.85; H, 4.58; N, 10.61. Found C, 75.83; H, 4.57; N, 10.84

1-methyl-4, 6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridine (5), 64% yield; M.P. 153-54 °C; IR (KBr) (v ***cm^{-1}):*** 3060,3020,2 920,1590,1570,1480,1460,750,690,680. ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 4.15(3H,s,N-CH_3);6.80(1H,s,H-3); 7.20-8.20(11H,m, ArH&H-5) Anal.Calcd.for $C_{19}H_{15}N_3$ (Mw 285) C, 79.97; H, 5.30; N, 14.72.Found C, 80.01; H, 5.32; N, 14.84

Method B

A mixture of 10mmoles of 5-amino-3-methyl-l-phenylepyrazole, 10mmole of a benzaldehyde and a few drops of concentrated hydrochloric acid and 15-20 mL absolute ethanol was held under reflux for three hours to give a Schiff's base[16], followed by addition of 10mmoles of acetophenone. The reaction mixture was heated under reflux for a further three hours period. On cooling the reaction mixture was poured over crushed ice (100g) and the precipitates were filtered and crystallized from ethanol to give the desired products **6-11**.

One pot reaction

An equimolar (5 mmoles) mixture of an arylaldehyde and acteophenone and a 5-aminopyrazole in 100mL acetic acid was heated under reflux for 6 hours. After cooling, the mixture was poured over excess water, the precipitates obtained were filtered and crystallized from ethanol to give the desired 4, 6-diarylpyrazolo [3, 4-*b*] pyridines in over 80% yield. These were identical with the products of stepwise reaction above.

3-methyl-6-(2-nitrophenyl)-1,4-diphenyl-1*H*-pyrazolo [3, 4-b] pyridine (6) this compound was obtained in 60% yield; M.P. 160 °C; IR (KBr) (v ***cm^{-1}):*** 2920, 1570, 1500,1560,1450,1340 (NO_2),1020. ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 1.25 (3H,s,CH_3);7.80-9.85(15H,m,ArH&H-5) Anal. Calcd.for $C_{25}H_{18}N_4O_2$ (Mw 406) C, 73.98; H, 4.43; N, 13.79. Found C, 73.93; H, 4.35; N, 13.82

3-methyl-6-(2-methoxyphenyl)-1,4-diphenyl-1H**-pyrazolo[3,4-**b**]pyridine (7)** this compound was obtained in 65% yield; M.P. 218 °C; IR (KBr) (v cm^{-1}): 2800, 1700, 1650, 1510, 1090,635. ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 1.20(3H,s,CH_3);3.75 (3H,s,OCH_3), 8.20-9.05 (15H,m, ArH,&H-5) Anal.Calcd.for $C_{26}H_{21}N_3O$ (Mw 391) C, 79.80; H, 5.37; N, 10.74 Found C, 80.20; H, 5.40; N, 10.70

3-methyl-6-(2-bromophenyl)-1,4-diphenyl-1H**-pyrazolo[3,4-**b**]pyridine (8)**, 72% yield; M.P. 160 °C; IR (KBr) (v cm^{-1}): 1750, 1630, 1570, 1520, 660, 470. ^1H NMR ($CDCl_3$), δ ppm(J, Hz) : 2.14 (3H,s,CH_3); 7.87-9.80

(15H,m,ArH& H-5) Anal.Calcd.for $C_{25}H_{18}BrN_3$ (Mw 439) C, 68.18; H,4.05; N, 9.55 Found C, 68.08; H, 4.25; N, 9.05

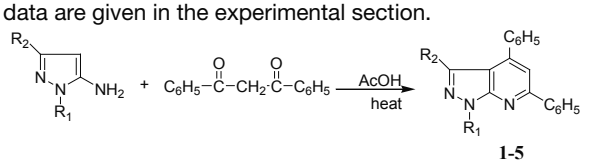
3-methyl-6-(2-chlorophenyl)-1,4-diphenyl-1H-pyrazolo[3,4-b]pyridine (9), 74% yield; M.P. 154 °C; IR (KBr) (v cm^{-1}): 1640, 1570, 1530, 848, 630. Anal.Calcd.for $C_{25}H_{18}ClN_3$ (Mw 395) C, 75.85; H, 4.58; N, 10.61 Found C, 75.68; H, 4.51; N, 10.58

3-methyl-6-(2, 4-dichlorophenyl)-1,4-diphenyl-1H-pyrazolo[3,4-b]pyridine (10), 70% yield; M.P. 130 °C; IR (KBr) (v cm^{-1}): 1740, 1610, 1580, 1510, 850, 710. Anal. Calcd.for $C_{25}H_{17}Cl_2N_3$ (Mw 429) C, 69.77; H, 3.95; N, 9.77 Found C, 69.73; H, 3.91; N, 9.72

3-methyl-6-(2-hydroxyphenyl)-1,4-diphenyl-1H-pyrazolo[3,4-b]pyridine (11), 73% yield; M.P. 260 °C; IR (KBr) (v cm^{-1}): 3160, 2820, 2280, 1730, 1650, 1620, 1515, 1070, 630. ^{1}H NMR ($CDCl_3$), δ ppm(J, Hz) : 1.20 (3H,s,CH_3);8.10-8.90 (15H,m,ArH& H-5) Anal.Calcd.for $C_{25}H_{19}N_3O$ (Mw 377) C, 79.58; H, 5.04; N, 11.14 Found C, 79.52; H, 5.12; N, 11.17

RESULTS AND DISCUSSIONS

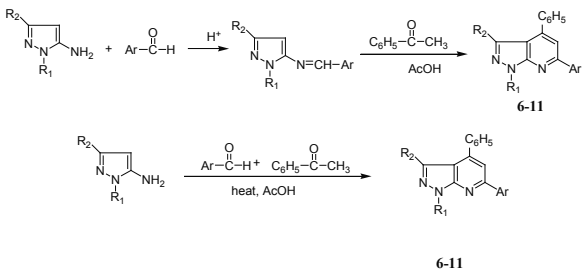
During this work various 4,6-diarylpyrazolo[3,4-*b*]pyridines were prepared from 5-aminopyrazoles' reaction with 1,3-dicarbonyl compounds (Combe's method[12]) or with aromatic aldehydes and ketones (modified Doebner's method[13]).As for the symmetrically substituted 4,6-diarylpyrazolo[3,4-*b*]pyridines, 5-aminopyrazoles were condensed with a 1,3-dicarbonyl compound-dibenzoyl methane. Our earlier attempts employing zinc chloride catalyst in this reaction had failed to give satisfactory results but now employing acetic acid as the solvent as well as the acid catalyst gave the desired products in excellent yields (upto 78%) (scheme I). The di-and triaryl substituted pyrazolo[3,4-*b*]pyridines thus obtained and their spectral data are given in the experimental section.



1-5

Scheme 1

For the synthesis of 4,6-diarylpyrozolo [3,4-*b*] pyridines bearing different aryl rings at 4- and 6- positions, however , Doebner's modified method (method B) was used (scheme 2) and various arylated derivatives were obtained in good yields. Reaction of acetophenone with preformed schiff's bases from 5-amino pyrazoles and arylaldehydes or alternatively in a one pot reaction of 5-amino pyrazoles with an aromatic aldehyde and acetophenone afforded the products **6-11**(method B), their respective element analyses and spectral data are given in the experimental section. The products in both these reactions: stepwise or "one pot" were identical in all respects (TLC, MP, IR and NMR spectra).



6-11

Scheme 2

The Doebner's method has the advantage of introducing the desired aryl groups at the 4- and 6-position of pyrazolo [3, 4-*b*] pyridine ring by varying aromatic aldehydes and ketones. Further work on these syntheses is in progress.

The ^{1}HNMR Spectra were helpful in characterizing the products. It was noted that the methyl protons at 3- position of some of the products demonstrated shielding effect of upto 1ppm due to the aryl group at 4- position. This shielding effect has also been observed earlier in other annealed pyrazole systems [9, 14, 15].

Antibacterial activity

Antibacterial activity of Diraylpyrazolo[3,4-*b*]pyridines (**1-11**) was tested by Agar plate disc diffusion method[17] against six different bacterial strains; *Staphylococcus aureus* (gram +ve), *Pseudomonas* (gram –ve), *Escherichia coli* (gram –ve) and *Klebsiella* (gram –ve). The filter paper disc (6.00 mm in diameter) was soaked with the solution of 50 mg of compound in 1 mL of chloroform was placed in the centre of plate. The plates were incubated with the growing cultures of bacterial strains.

The four different types of bacterial cultures were inoculated and were further incubated at 37°C for 24-48 hours. Vibramycin and Cefizox were used as standards. The test organism *S.aureus* and *E. coli* showed an inhibition zone of (30 mm) for Vibramycin while *Pseudomonas* showed resistance. *Klebsiella* showed an inhibition zone of (10 mm) for Vibramycin and (20 mm) for Cefizox, while in case of Cefizox no antibacterial activity was observed in *S. aureus* and *E. coli* but *klebsiella* showed an inhibition zone of 20 mm.

In case of antibacterial activity of synthesized compounds (**1-11**), only four compounds **2, 6, 7** and **8** showed moderate activity against *S.aureus*, *Klebsiella*, *Pseudomonas* and *E. coli*. The results of antibacterial activity are given in **Table-1.**

Table 1. Antibacterial Activity of Diraylpyrazolo[3,4-*b*]pyridines 1-11

Compound No.	*S.aureus*	*Klebsiella*	*Pseudomonas*	*E. coli*
1	-	-	-	-
2	10	-	12	-
3	-	-	-	-
4	-	-	-	-
5	-	-	-	-
6	10	10	-	-
7	-	-	-	10
8	-	-	15	-
9	-	-	-	-
10	-	-	-	-
11	-	-	-	-
VIB	30	10	-	30
CEF	-	20	-	-

VIB: Vibramycin, CEF: Cefizox

CONCLUSIONS

The method used for the synthesis of Diraylpyrazolo[3,4-*b*] pyridines is a mild and efficient one as it gives better yields (60-75%). Schiff's bases being the reactive intermediate, their preformation or *in situ* formation both gave satisfactory results. The synthesized compounds showed moderate activity against some bacterial strains.

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